

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/B2004/004363

International filing date (day/month/year)
22.12.2004

Priority date (day/month/year)
22.12.2003

International Patent Classification (IPC) or both national classification and IPC
C07C231/10, C07C233/00

Applicant
PPG-SIPSY

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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**WRITTEN OPINION OF THE
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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and Industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 10, 11

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 10, 11

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

☐ has not been furnished

☐ does not comply with the standard

the computer readable form

☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

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Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:
- ☐ paid additional fees.
 - ☐ paid additional fees under protest.
 - ☒ not paid additional fees.
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
- ☒ not complied with for the following reasons:
- see separate sheet**
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☐ all parts.
 - ☒ the parts relating to claims Nos. 1-9

Box No. V Reasoned statement under Rule 43b/s.1(a)(i) with regard to novelty, Inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	3,9
	No: Claims	1,2,4-8
Inventive step (IS)	Yes: Claims	
	No: Claims	1-9
Industrial applicability (IA)	Yes: Claims	1-9
	No: Claims	

2. Citations and explanations

see separate sheet

**WRITTEN OPINION OF THE
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AUTHORITY (SEPARATE SHEET)**

International application No.

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Re Item IV

Lack of unity of invention

This Authority considers that there are 2 inventions covered by the claims indicated as follows:

first invention : Claims 1-9 directed to the process for the preparation of enamides of formula (I) according to claim 1.

second invention: Claims 10 and 11 directed to the use of the enamides of formula (IIE) according to claim 10 in an hydrogenation reaction to prepare amine or amide derivatives.

The reasons for which the inventions are not so linked as to form a single general inventive concept, as required by Rule 13.1 PCT, are as follows:

In order to be unitary, the group of claims must be so linked as to form a single general inventive concept. This requirement is fulfilled when all the claims share the same or corresponding special technical features. These features are those which define a contribution made by the invention over the prior art (Rule 13.2 PCT).

In the present case the only common element linking claims 1-9 with claims 10 and 11 is the enamide of formula (IIE), which is a preferred embodiment of the compounds of formula (I). However, the enamides (IIE) which are used in hydrogenation reaction for the preparation of amine or amide derivatives of pharmaceutical interest are already known from the prior art (see e.g. the specific compound 29 in XP001069473). Thus, the enamides (IIE) cannot be considered the special technical feature required by Rule 13.2 PCT because it is already known.

Moreover, the technical problem addressed by claims 1-9 appears to be the provision of a process for preparing enamides of formula (I), whereas the technical problem to be addressed by claims 10 and 11 appears to be the use of enamides of formula (IIE) in an hydrogenation reaction to prepare amine or amide derivatives of pharmaceutical interest.

As the technical problems are not the same or corresponding, the requirements of unity are not fulfilled.

The application has been divided into the above two inventions which individually are considered to meet the requirement of unity.

Re Item V

**Reasoned statement with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement**

1. Novelty, Article 33(2) PCT of first invention (CLAIMS 1-9):

The following documents (D) are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

- D1: US-A-4 194 050 (HAZAMA MOTOO) 18 March 1980
- D2: WO 99/18065 A (CHIROTECH TECHNOLOGY LTD) 15 April 1999
- D3: Z.ZHANG, G.XHU, Q.JIANG, D.XIAO, X.ZHANG: "Highly enantioselective hydrogenation of cyclic enamides catalized by Rh-PennPhos Catalyst" JOURNAL OF ORGANIC CHEMISTRY, vol. 64, 1999, pages 1774-1775, XP002280541
- D4: BURK, MARK J. ET AL: "A Three-Step Procedure for Asymmetric Catalytic Reductive Amidation of Ketones" JOURNAL OF ORGANIC CHEMISTRY, 63(18), 6084-6085, 1998, XP002280540
- D5: LI, WENGE ET AL: "Synthesis of Chiral Hydroxyl Phospholanes from D-mannitol and Their Use in Asymmetric Catalytic Reactions" JOURNAL OF ORGANIC CHEMISTRY, 65(11), 3489-3496, 2000, XP001069473

With regard to the prior art disclosed in the documents cited above the subject-matter of the present application, i.e the hydrogenation/isomerisation of the oxime of formula (II) in presence of a heterogeneous catalyst for the preparation of enamides of formula (I), does not appear to fulfil the requirements of novelty, cf, Article 33(2) PCT.

Document D1 describes already the hydrogenation / isomerisation of an oxime compound in the presence of a Ru-carbon or Ru-alumina catalyst.

The reaction described in D2-D4 consists also in a hydrogenation / isomerisation of an oxime compounds in the presence of an iron-catalyst.

The subject-matter of present claims 1-2 and 4-8 has been anticipated by D1-D4 and thus, the requirements of Article 33(2) PCT are not considered to be met.

However, the subject-matters of claims 3 and 9 are novel over D1-D4 on account of the

specific heterogeneous catalyst used in the process (Pd, Ir, Pt, Rh, Ni catalysts) in claim 3 and on account of the organic mineral salts used for the washing step in claim 9.

2. Inventive step, Article 33(3) PCT:

The present application concerns the process for the preparation of enamides of formula (I) by hydrogenation/isomerisation of the corresponding oxime compounds. This reaction is performed in the presence of a heterogeneous Pd, Ir, Pt, Rh or Ni catalyst. D1 discloses the hydrogenation/isomerisation reaction in the presence of a Ru-catalyst and D2-D4 disclose the reaction in presence of a Fe-catalyst.

Thus, the skilled person looking for a further process for the preparation of enamides would start from D2 and D1 and continue on the next column of the periodic table system and try the reaction with a Rh, Ir, Pb or Pt catalyst. Thus, the present claimed process can be considered as an obvious modification/alternative of the process disclosed in D1.

The problem underlying the present application is therefore to be seen in the development of an improved and easily scaled-up process with regard to the process of D1.

However, the present application does not contain any evidence for an unexpected effect compared to the process of D1 and especially it was not shown that the claimed process provides the alleged advantages recited on p.2, l.1-8.

In the absence of evidence for such surprising effect, the subject-matter of the present application cannot be considered to satisfy the requirements of Article 33(3) PCT.

Furthermore, it should be pointed out that it must be made credible that essentially all of the claimed matter solves the above given technical problem: a sufficiently clear disclosure of an invention presupposes that it enables the skilled person to obtain substantially all embodiments falling within the ambit of the claims. The scope of claim 1 is therefore considered to be unlimited and thus purely speculative with regard to the examples provided. Indeed, the definitions of the substituents R1-R4 in claim 1 cannot be considered to be a reasonable generalisation of the examples provided in the description and are considered to be unclear (Article 6 PCT) due to the use of open-ended expressions like "being substituted or not with a functional group" or "alkyl", "heterocycle" etc, without further limitation of the number of elements included within. These broad definitions imply that a considerable number of compounds of formula (I) can be prepared according to the process of claim 1; Adaptation of the claimed process going beyond the scope of the invention would be necessary to

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prepare a lot of compounds as defined in claim 1.

An inventive step in the sense of Art. 33(3) PCT in conjunction with Art. 6 PCT cannot be acknowledged over the whole claimed scope.